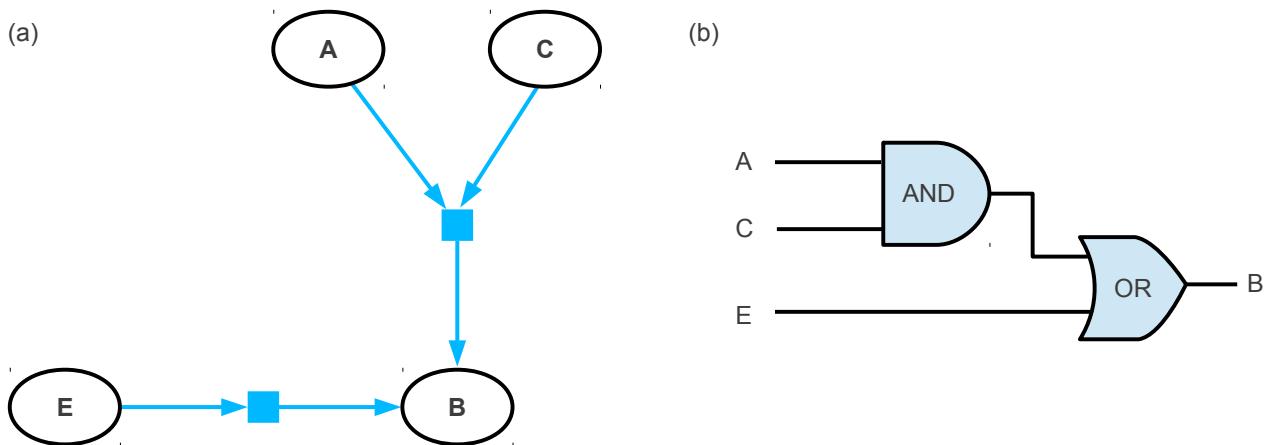
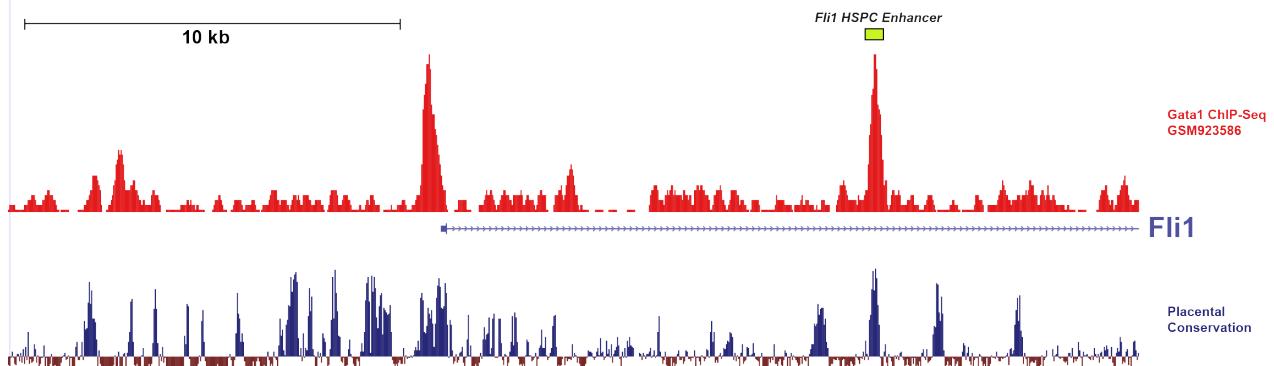


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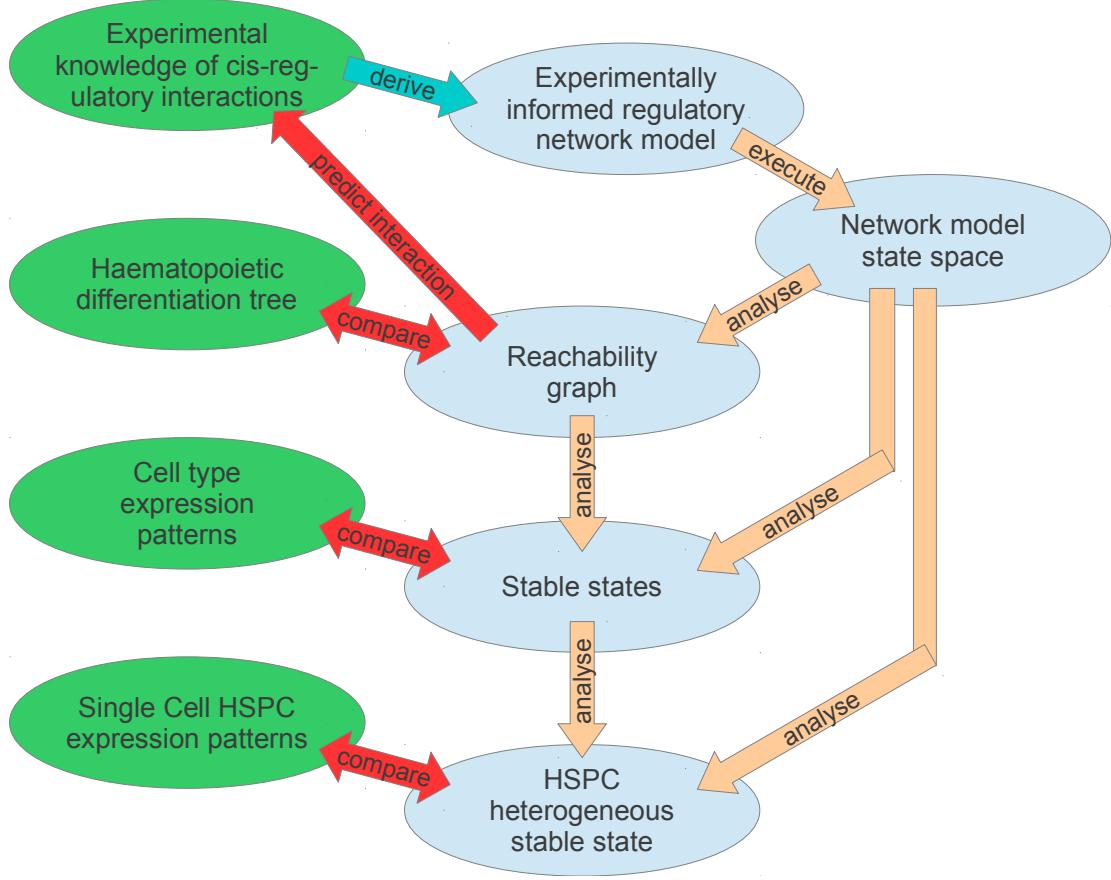


Supplementary Figure S1. (a) A sample Boolean GRN. The node B is either activated by E or by simultaneous effect of node A and node C. (b) GRN mapped onto Boolean functions.



Supplementary Figure 2: The Fli1 +12 kb HSPC enhancer is bound by Gata1 in fetal liver derived progenitors co-expressing both Gata1 and Fli1.

Shown is a screenshot of Gata1 ChIP-Seq result (from NCBI GEO accession GSM923586) across the 5' portion of the mouse Fli1 gene locus using the UCSC genome browser. The Fli1 +12 HSPC enhancer region is indicated by a green box. The red custom track shows the ChIP-Seq density profile for Gata1 with very clear peaks of enrichment over the promoter and the +12 HSPC enhancer region within intron 1 of Fli1. At the bottom is the UCSC track for placental mammal sequence conservation, illustrating the high evolutionary DNA sequence conservation at the +12 HSPC region.



Supplementary Figure 3: A schematic overview of our analysis pipeline. Experimental parts are in green, modelling is in blue. We start from the experimental knowledge of interactions from which the model is built. Subsequent analysis of the model state space yields predictions in terms of interactions, reachability, stable states and expression patterns. Finally, these are compared with experimental data.

SUPPLEMENTARY TABLES:

Table S1: Summary of genes included in the network model. We list the name used, the Mouse Genome Informatics (MGI) database¹ ID, common name and synonyms according to the MGI-db.

Gene	ID	Name	Synonyms
Erg	MGI:95415	avian erythroblastosis virus E-26 (v-ets) oncogene related	D030036I24Rik
Eto2 (Cbfa2t3)	MGI:1338013	core-binding factor, runt domain, alpha subunit 2, translocated to, 3 (human)	A630044F12Rik, Eto2, ETO-2, MTGR2
Fli1	MGI:95554	Friend leukemia integration 1	EWSR2, Fli-1, Sic1, SIC-1
Gata1	MGI:95661	GATA binding protein 1	Gata-1, Gf-1
Gata2	MGI:95662	GATA binding protein 2	Gata-2
Hhex	MGI:96086	hematopoietically expressed homeobox	Hex, Hex1, Hhex-rs2, Prhx
Pu.1 (Sfpi1)	MGI:98282	SFFV proviral integration 1	Dis-1, PU.1, Sfpi-1, Spi-1, Tcfpu1, Tfpu.1
Runx1	MGI:1338013	runt related transcription factor 1	AML1, Cbfa2, Pebp2a2, runt domain, alpha subunit 2
Scl (Tal1)	MGI:98480	Stem Cell Leukemia	Tal1, bHLHa17, SCL/tal-1
Smad6	MGI:1336883	SMAD family member 6	Madh6, Smad 6
Zfpm1	MGI:1095400	zinc finger protein, multitype 1	Fog1, Friend of GATA-1

¹ Eppig JT, Blake JA, Bult CJ, Kadin JA, Richardson JE; the Mouse Genome Database Group. 2012. The Mouse Genome Database (MGD): comprehensive resource for genetics and genomics of the laboratory mouse. Nucleic Acids Res 2012; 40(1):D881-86

Table S2: Summary of interactions in the network model. Prerequisites are the input gene(s), which can be one or two genes. Interactions are either activating or inhibiting. For each interaction, primary literature is referenced in the final column, the list of references appears below the table. The predicted and experimentally validated inhibition of Fli1 by Gata1 that was added in the refined model is indicated in red.

Prerequisites	Interaction	Target	Reference
Fli1	ACTIVATION	Pu.1	(Starck et al., 1999)
Pu.1 + Gata1	INHIBITION	Gata1	(Zhang et al., 2000)
Gata1 + Pu.1	INHIBITION	Pu.1	(Nerlov et al., 2000)
Gata1 + Zfpm1	INHIBITION	Gata2	(Crispino et al., 1999)
Fli1 + Gata2	ACTIVATION	Scl	(Gottgens et al., 2002)
Fli1	ACTIVATION	Gata2	(Pimanda et al., 2007b)
Scl + Gata1	ACTIVATION	Scl	(Ogilvy et al., 2007)
Scl + Gata2	ACTIVATION	Gata2	(Johnson et al., 2012; Khandekar et al., 2007)
Scl + Gata1	ACTIVATION	Gata1	(Vyas et al., 1999)
Gata2 + Scl	ACTIVATION	Zfpm1	(Wilson et al., 2010; Wilson et al., 2009)
Gata2 + Scl	ACTIVATION	Scl	(Ogilvy et al., 2007)
Fli1	ACTIVATION	Scl	(Gottgens et al., 2002)
Fli1	ACTIVATION	Fli1	(Donaldson et al., 2005)
Gata2	ACTIVATION	Fli1	(Donaldson et al., 2005)
Fli1	ACTIVATION	Erg	(Thoms et al., 2011)
Erg	ACTIVATION	Fli1	(Pimanda et al., 2007b; Wilson et al., 2010)
Erg	ACTIVATION	Erg	(Thoms et al., 2011)
Scl + Eto2	INHIBITION	Erg	(Schuh, 2005; Thoms et al., 2011)
Scl + Gata2	ACTIVATION	Fli1	(Pimanda et al., 2007b)
Gata2	ACTIVATION	Erg	(Thoms et al., 2011)
Runx1	ACTIVATION	Runx1	(Nottingham et al., 2007)
Pu.1	ACTIVATION	Runx1	(Nottingham et al., 2007)
Runx1	ACTIVATION	Pu.1	(Huang et al., 2008)
Gata2 + Scl	ACTIVATION	Runx1	(Nottingham et al., 2007)
Fli1	ACTIVATION	Runx1	(Nottingham et al., 2007)
Erg	ACTIVATION	Runx1	(Taoudi et al., 2011)
Pu.1	ACTIVATION	Pu.1	(Chen et al., 1995)
Scl + Gata2	ACTIVATION	Eto2	(Wilson et al., 2010; Wilson et al., 2009)
Runx1 + Smad6	INHIBITION	Runx1	(Pimanda et al., 2007a)
Erg	ACTIVATION	Smad6	(Knezevic et al., 2011)
Fli1	ACTIVATION	Smad6	(Knezevic et al., 2011)
Scl + Gata2	ACTIVATION	Smad6	(Knezevic et al., 2011)
Erg	ACTIVATION	Scl	(Gottgens et al., 2002; Rainis et al., 2005)
Scl + Gata2	ACTIVATION	Hhex	(Donaldson et al., 2005; Wilson et al., 2009)
Gata2 + Hhex	INHIBITION	Gata2	(Kobayashi-Osaki et al., 2005; Minami et al., 2004)
Fli1	ACTIVATION	Hhex	(Donaldson et al., 2005)
Erg	ACTIVATION	Hhex	(Oram et al., 2010)
Runx1	ACTIVATION	Erg	(Thoms et al., 2011; Wilson et al., 2010)
Erg	ACTIVATION	Gata2	(Taoudi et al., 2011)
Gata1	INHIBITION	Fli1	This work

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Table S3: Summary of state space paths compared to paths in the developmental tree. Shown are the closest states that connect to a particular differentiated state, i.e. all shortest transition paths allowed by our transcription regulatory network model between each of the cell type states considered. HSPC-S-1 refers to the stable state S-1 (see also Figure 2A in the main text) that contains the expected pattern of the HSPC cell type together with 31 additional interconnected network states. In the table, intermediate states are indicated by their bit-map expression states for the 11 genes (in alphabetical order: Erg Eto2 Fli1 Gata1 Gata2 Hhex Pu.1 Runx1 Scl Smad6 Zfpml). The ‘x’-es denote gene states that can be ‘on’ (1) or ‘off’ (0) in a correlated fashion (i.e., Gata2 and Runx1 both ‘on’ or both ‘off’).

	Starting Cell type	‘Push’ distance	‘Push’ intermediate state	Transition path length	Target Cell type
On path (11):					
	HSPC	2	11011111111	5	Erythroid
	HSPC-S-1	2	01010111111	3	Erythroid
	HSPC	3	01101111001	2	Monocyte
	HSPC-S-1	2	0110x11x000	1	Monocyte
	HSPC	1	11101111101	2	Granulocyte
	HSPC-S-1	1	-	0	Granulocyte
	HSPC	3	01101111001	1	B-Cell
	HSPC-S-1	2	0110x11x001	1	B-Cell
	HSPC	4	01101101001	1	NK
	HSPC-S-1	3	0110x10x001	1	NK
	HSPC	4	01101101001	2	CD4
	HSPC-S-1	3	0010x10x001	1	CD4
	CD4	1	-	0	CD4-activated
	HSPC	4	01101101001	7	CD4-activated
	HSPC	3	01101111001	2	CD8
	HSPC-S-1	2	0010x11x001	1	CD8
	CD8	4	-	0	CD8-activated
	HSPC	4	01101101001	8	CD8-activated
Upstream (11):					
	Erythroid	-		5	HSPC
	Monocyte	-		5	HSPC
	Granulocyte	-		3	HSPC
	B-Cell	-		4	HSPC
	NK	-		5	HSPC
	CD4	-		6	HSPC

Starting Cell type	'Push' distance	'Push' intermediate state	Transition path length	Target Cell type
CD4-activated	-		1	CD4
CD4-activated	-		7	HSPC
CD8	-		5	HSPC
CD8-activated	-		3	CD8
CD8-activated	-		8	HSPC
Across (18):				
B-Cell	-		1	CD8
B-Cell	-		1	Monocyte
CD4	-		1	CD8
CD8-activated	-		1	CD4-activated
NK	-		1	B-Cell
NK	-		1	CD4
CD4-activated	-		2	CD8
CD8	-		2	Granulocyte
CD8-activated	-		2	CD4
NK	-		2	CD8
NK	-		2	Monocyte
B-Cell	-		3	Granulocyte
CD4	-		3	Granulocyte
CD4-activated	-		4	Granulocyte
Erythroid	-		4	Granulocyte
NK	-		4	Granulocyte
CD8-activated	-		5	Granulocyte
Monocyte	-		6	Granulocyte